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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,646	02/22/2002	Robert Norman Rice	37921-2	1954

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EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,646	RICE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. The use of the trademarks TAQ, DYNABEADS, Opti-MEM, GENETICIN, BECKMAN, FALCON, EPPENDORF, RPMI, UNIVAR, AMBION, SIGMA, DYNAL, TAQMAN have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

4. The specification is objected to as documents have been improperly incorporated by reference. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is

> effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

While the instant disclosure does identify documents and asserts that they have been incorporated by reference, the disclosure does not identify what material is being incorporated and what parts of the cited documents are being incorporated. Accordingly, the documents have not been considered to have been incorporated by reference.

Claim Objections

5. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim that depends from a dependent claim should not be separated by any claim that does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n). In the present case dependent claim 5 is separated from independent claim 1 by independent claim 4; dependent claims 10-21 are separated from

independent claim 6 by claims 8 and 9; and dependent claims 24-27 are separated from independent claim 22 by independent claim 23.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (Quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth

as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

8. Attention is directed to claim 1, reproduced, below.

1. (Currently amended) A method for determining the rate of transcription of a transcriptional unit in a composition of cells, said method comprising:

lysing the cells and obtaining from the cells a preparation of nuclei comprising said transcriptional unit with nascent RNA strands attached thereto and placing same on ice to temporarily inhibit continued transcription and then placing said nuclei under conditions to permit transcription of the transcriptional unit in the presence of biotin-16-UTP, wherein said biotin-16-UTP includes a cleavable linker between the biotin and the UTP, to thereby provide a population of biotin-labeled nascent transcripts; and

isolating said biotin-labeled nascent transcripts by immobilizing same onto streptavidin-labeled iron beads, cleaving said biotin-16-UTP at said cleavable linker to thereby provide a population of nascent RNA transcripts and purifying ~~same~~ said RNA transcripts by magnetic separation and quantitatively determining the level of ~~specific biotin-labeled~~ the RNA transcripts by subjecting the ~~biotin-labeled~~ RNA transcripts to real-time PCR.

It is noted with particularity that one is to first isolate the transcripts by "immobilizing same onto streptavidin-labeled iron beads," then cleave the RNA transcripts from the iron beads, and then somehow purify and separate and quantify the RNA transcripts using "magnetic separation" The last step of "magnetic separation" is seemingly impossible to achieve as the RNA transcripts have already been cleaved from the iron particles. With the RNA transcripts (and amplicons) lacking any magnetizable marker, one cannot then use a magnet to separate them.

A review of the disclosure fails to find a reproducible method whereby such a combination of steps can be performed. Absent such requisite guidance, the skilled artisan would have to resort to trial-and-error experimentation. Such efforts do not constitute routine experimentation, which is permitted, but rather, rise to the level of undue experimentation. Accordingly, and in the absence of convincing evidence to the contrary, the specification has not been found to enable the method of claims 1-3 and 5.

9. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. For convenience, claims 22 and 23, the only independent claims in the present rejection, are reproduced below.

22. (New) A kit for determining the rate of transcription of a transcriptional unit in one or more cells, said kit comprising:

enzymes, buffers, and diluents for obtaining nucleic acids;

biotin-labeled ribonucleotides, wherein said biotin-labeled ribonucleotides include a cleavable linker between said biotin and said ribonucleotide;

enzymes, buffers, and diluents for transcription of nucleic acids;

a solid matrix;

enzymes, buffers, and diluents for isolating biotin-labeled molecules using said solid matrix; and

enzymes, buffers, and diluents for real time polymerase chain reaction.

23. (New) A kit for determining the rate of transcription of a transcriptional unit in one or more cells, said kit comprising:

enzymes, buffers, and diluents for obtaining nucleic acids;

biotin-labeled ribonucleotides;

enzymes, buffers, and diluents for transcription of nucleic acids;

a solid matrix, wherein said matrix includes a cleavable linker;

enzymes, buffers, and diluents for isolating biotin-labeled molecules using said solid matrix, wherein said matrix includes a cleavable linker; and

enzymes, buffers, and diluents for real time polymerase chain reaction.

It is noted with particularity that the kits of claims 22 and 23 are to comprise enzymes for a) "obtaining nucleic acids;" b) "for transcription of nucleic acids;" c) "isolating biotin-labeled molecules using said solid matrix;" and d) "for real time [*sic*] polymerase chain reaction."

At page 8, sixth paragraph, of the response of 21 April 2003 states in part:
Support for claims 22-27 may be found at page 23 [sic] line 27 through page 26, line 28 and page 28 [*sic*] line 10 through page 29 [*sic*] line 2." While the specification has been found to suggest a variety of possible configurations, the disclosure has not been found to provide an adequate written description of enzymes that are to be used when "obtaining nucleic acids" from any source. The disclosure has not been found to provide an adequate written description of a plurality of enzymes to be used for "transcription;" and no enzyme has been adequately described that is to be sued in the isolation of biotin-labeled molecules using a solid support. An adequate written description has been found for but one enzyme, and that being thermostable DNA polymerase TAQ.

10. It is noted that the subject application discloses cleavage of a disulfide bond between biotinylated UTP and an iron bead with the use of dithiothreitol (DTT), not with an enzyme. No enzyme was being used or otherwise provided to effect transcription but rather, the cells under evaluation were conducting transcription as part of their normal physiological processes and it is the RNA so produced by the cells that is being isolated, amplified, and quantified. Additionally, no enzyme was used in the isolation of nucleic acids but rather, sucrose buffers (see Buffers A, B, C, and D at pages 43-45 of the disclosure).

While one may assert that it would have been obvious to one of skill in the art at the time the invention was made to have selected various components and to have placed them in a kit, along with the pertinent instructions, such an argument does not render moot the need for the disclosure to provide an adequate written description of the invention. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

Accordingly, broad assertions as to what is to be found in the kit, while motivating, does not reasonably suggest that applicant had possession of just such genera of kits as is now claimed.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 2, 3, and 5-21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1-3 and 5-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps that will result in the actual determination of the rate of transcription of a transcriptional unit. As presently worded, one is to somehow determine the rate of transcription of any transcriptional unit by conducting polymerase chain reaction (PCR). PCR will only produce or amplify the amount of template present, it does not, in and of itself, require any measurement of any amplicon, much less a determination of any rate of transcription. In order to perform a rate determination a correlation needs to be made between the amplicons produced, if any, and some other fixed point. Such steps are not recited and the mere production of an otherwise undetectable product cannot yield the required end product.

14. The term "real-time" in claims 1, 4, 6, 8, 22, and 23 is a relative term that renders the claim indefinite. The term "real-time" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Dependent claims 2, 3, 5, 7, 9, 10-21, and 23-27 fail t overcome this issue and are similarly rejected.

15. Claims 6 and 18-20 are indefinite with respect to just how the term "exposing" is to be interpreted; see dependent claim 18 at line 5. Do the cells need to be transfected with something or is it enough that it is in the same room, state or country in order for there to be "exposure?" While claim 6 does not recite this term, claim 18 does depend from said claim 6 and as such claim 6 hs been interpreted as fairly encompassing this embodiment.

16. Claim 19 is confusing as to how the portions of cells are exposed to "endogenous genes." Is it enough that the cells have a plethora of genes naturally or from another source being

introduced into the cell. Additionally, if the gene is from another source, is it enough that the cells/life form be in some proximity to the cell portions under study in order for there to be the requisite "exposure?"

17. Claim 20 is indefinite with respect to what constitutes a "trangene." Perhaps applicant had intended --transgene--.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Burmer et al. (US 5,935,788).

20. Burmer et al., column 10, first full paragraph, disclose kits that are to comprise any reagent for the disclosed methods, as well as instructions. One of the methods disclosed by Burmer et al., is PCR; see column 7, third paragraph. Accordingly, the kit of Burmer et al., is considered to have as an inherent property "one or more buffers, diluents and enzymes in single or multiple components."

21. While Burmer et al., do not disclose the claimed method that is to be recorded on the instructions, the text of the printed material of the instant instructions is not considered to alter

the functionality of the substrate upon which it is printed. Accordingly, the text found on the claimed instructions has no patentable weight. *In re Gulack* (CAFC, 1983) 217 USPQ 401[1].

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

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[1] Gulack, quoting from the decision of the Board of Patent Appeals and Interferences:

> Unlike the fact in Miller, the printed indicia claimed herein [convey] no meaningful information in regard to the substrate [they are] arranged on, [do] not require any size relationship of the substrate, and [do] not require any particular substrate to effectively convey the information. We are convinced that *there is no functional relationship between appellant's indicia and the claimed endless band.*
>
> ***In our opinion, the endless loop formed by the hatband with numerical digits printed thereon is the same structure claimed by appellant and *the sole difference is in the content of the printed material.* Accordingly, *there being no functional relationship of the printed material to the substrate, as we have noted above, there is no reasons* [sic] *to give patentable weight to the content of the printed matter which, by itself, is non-statutory subject matter.*

24. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
June 10, 2003